PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 150387/KB	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/CZ2004/000078	International filing date *(day/month/year)* 23.11.2004	Priority date *(day/month/year)* 25.11.2003
International Patent Classification (IPC) or national classification and IPC A61K31/58, A61K9/28, A61K9/20, A61K9/48		
Applicant PLIVA-LACHEMA A.S.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.08.2005	24.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schifferer, H Telephone No. +49 89 2399-7472

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CZ2004/000078

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 2, 4-7	as originally filed
3	received on 27.08.2005 with letter of 25.08.2005

Claims, Numbers

5-7	as originally filed
1-4	received on 27.08.2005 with letter of 25.08.2005

Drawings, Sheets

1/1	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CZ2004/000078

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-7
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Corrections - Rule 91 PCT
The change of the preposition from "spraying to the fluid bed" into "spraying in the fluid bed" in claim 1 and page 3 of present description is considered to fulfill the requirements of Rule 91 PCT.

2) Clarity
The clarity objections in 1.1 and 1.2 on the basis of Article 6 PCT have sufficiently been dealt with and explained in the Applicant's letter of July 15th, 2005.

3) Documents
The following documents (D1-D4) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 99/08684 A (GLAXO GROUP LIMITED; PARR, ALAN, FRANK; RIZZOLIO, MICHELE, CATHERINE) 25 February 1999 (1999-02-25)
D2: US 6 294 192 B1 (PATEL MAHESH V ET AL) 25 September 2001 (2001-09-25)
D3: US 2003/064097 A1 (PATEL MAHESH V ET AL) 3 April 2003 (2003-04-03)

Unless otherwise specified, reference is made to the respective cited passages in D1-D4 (see the International Search Report, Form PCT/ISA/210).

4) Novelty - Article 33 (1) and (2) PCT
4.1) D1-D3 disclose compositions comprising finasteride and a surfactant in formulations suitable for oral administration. However, none of said documents exactly describes the sequel of the following steps in manufacturing: 1. milling of a suspension comprising finasteride and an anion surfactant to a defined particle size, 2. spraying said suspension in a fluid bed onto a solid particle hydrophilic carrier.

4.2) In the light of D1-D3 (see sections V-3, 4.1) and under consideration of sections V-1.,2., the subject-matter of claims 1-7 seems to be novel according to Article 33 (1) and (2) PCT.

5) Inventive Step - Article 33 (1) and (3) PCT
5.1) The problem posed in the present application was the manufacturing of a finasteride solid dosage formulation with an instant release of the active agent enabling finasteride processing to the dosage form irrespectively of the size of its particles, i.e. also large finasteride particles.

The solution according to the Applicant was a pharmaceutical composition comprising finasteride and an anionic surfactant, whilst the manufacturing included 1. milling this aqueous suspension comprising finasteride and an anionic surfactant, 2. spraying this suspension onto a solid particle hydrophilic carrier in a fluid bed.

D2 which is regarded closest prior art discloses a pharmaceutical composition in form of tablets or capsules based on a solid carrier which contains a substrate and an encapsulation coat on the substrate, wherein the encapsulation coat comprises at least one pharmaceutical active ingredient (finasteride besides others) and at least one hydrophilic surfactant, such as sodium lauryl sulphate.

D1 does not disclose the concrete steps of manufacturing as follows:
1. milling an aqueous suspension comprising finasteride and an anionic surfactant,
2. spraying said suspension in a fluid bed on particles.

The Applicant's reply specifies that the addition of an anionic surfactant prior to spraying is to be regarded as a specific idea, since with this step a hydrophobic agent can be sprayed in an aqueous solution/suspension onto a hydrophilic particle.

5.2) Therefore, under provision of V-1., 2., the subject-matter of claims 1-7 does not seem to be obvious to a person skilled in the art due to the teaching of D2 or D1, D3, due to common textbook knowledge and galenical experience. Thus the aforementioned subject-matter seems to meet the requirements of Article 33 (1) and (3) PCT in that extent that it could be considered inventive.

6) Certain documents cited
On the basis of rule 70.10 PCT certain published documents - namely those published after filing /priority date of present application (Rule 64 (3) PCT) - should be mentioned as such. This refers to D4 demonstrating the following details:

Application No: PCT/IS2003/000034
Patent No: WO2004/047798
Publication date: 10.06.2004
Filing date: 21.11.2003
Priority date: 22.11.2002

D4 discloses a pharmaceutical composition in form of a tablet which comprises 0.1-10 wt % of finasteride, 0-10 wt% of sodium lauryl sulfate (as a wetting agent) and 0-90 wt% of microcrystalline cellulose. Tablets are manufactured using wet granulation. An exact sequel of the steps from milling to spraying of a suspension comprising finasteride and a surfactant is not given in D4.

CLAIMS

1. A method of preparation of an oral solid dosage form with instant release of an active agent containing as the active agent finasteride characterized in that that an aqueous suspension containing 5% to 50% by weight of finasteride, based on the total weight of the suspension, and 0.1% to 50% by weight of at least one anion surfactant, based on the weight of finasteride, is milled in order to reach such distribution of particle size of finasteride form that the size of 10 % of particles does not exceed 2 μm, the size of 50% of particles does not exceed 7 μm, and the size of 90 % of particles does not exceed 17 μm, then the obtained aqueous suspension is sprayed in a fluid bed onto a solid particle hydrophilic carrier having such distribution of particle size that the size of 90 % of particles exceeds 40 μm and the size of 10 % of particles exceeds 200 μm, and the size of 99% of particles does not exceed 300 μm.

2. The method according to Claim 1 characterized in that that at least one substance of the following: sodium sulfosuccinate, sodium lauryl sulfate, sodium hexadecylsulfate, sodium hexadecylsulfonate, and sodium dioctylsulfosuccinate is used as anion surfactant.

3. The method according to Claim 1 or Claim 2 characterized in that that a hydrophilic sugar, as sucrose, sorbitol, mannitol, glucose and lactose, native or modified starch and cellulose or their mixtures, particularly a mixture of lactose, microcrystalline cellulose and modified maize starch at the weight ratio of 142 : 86 : 11 are used as the solid particle hydrophilic carrier.

4. The method according to whichever of the Claims 1 through 3 characterized in that that a mixture obtained by the spraying of the aqueous suspension onto the solid particle hydrophilic carrier in the fluid bed is mixed with 2 to 10 % by weight, based on the total weight of the obtained mixtur, of at least one pharmaceutically acceptable hydrophilic lubricant showing an antistatic effect, such as colloidal silicon dioxide, sodium stearyl fumarate, polyethylene glycol or sodium lauryl sulfate.

SUBSTITUTE SHEET

Summary of the Invention

The subject-matter of this invention is a method intented for preparation of oral solid dosage form with instant release of an active agent containing as the active agent finasteride characterized in that that an aqueous suspension containing 5 to 50 % by weight of finasteride, based on the total weight of the suspension, and 0.1 to 50 % by weight of at least one anion surfactant, based on the weight of finasteride is milled in order to reach such distribution of particle size of finasteride that the size of 10 % of particles does not exceed 2 μm, the size of 50% of particles does not exceed 7 μm, and the size of 90 % of particles does not exceed 17 μm, then the obtained aqueous suspension is sprayed in a fluid bed onto a solid particle hydrophilic carrier having such distribution of particle size that the size of 90 % of particles exceeds 40 μm and the size of 10 % of particles exceeds 200 μm, and the size of 99% of particles does not exceed 300 μm.

At least one substance of the following: sodium sulfosuccinate, sodium lauryl sulfate, sodium hexadecylsulfate, sodium hexadecylsulfonate, and sodium dioctylsulfosuccinate is advantageously used as anion surfactant.

A hydrophilic sugar as sucrose, sorbitol, mannitol, glucose and lactose, native or modified starch, and cellulose or their mixtures, particularly a mixture of lactose, microcrystalline cellulose and modified maize starch at the weight ratio of 142 : 86 : 11 are advantageously used as the solid particle hydrophilic carrier.

The mixture obtained by the spraying of the aqueous suspension onto the solid particle hydrophilic carrier in the fluid bed is profitably mixed with 2 to 10 % by weight, based on the total weight of the obtained mixtur, of at least one pharmaceutically acceptable hydrophilic lubricant showing an antistatic effect, such as colloidal silicon dioxide, sodium stearyl fumarate, polyethylene glycol or sodium lauryl sulfate.

The mixture obtained by the spraying of the aqueous suspension onto the solid particle hydrophilic carrier in the fluid bed is advantageously mixed with 1 to 7 % by weight, based on the total weight of the obtained mixture, of at least one pharmaceutically acceptable disintegrant, such as ultraamylopectin, cross-linked sodium carboxymethylcellulose or cross-linked polyvinylpyrrolidone.

The mixture obtained by the spraying of the aqueous suspension onto the solid particle hydrophilic carrier in the fluid bed, optionally after being mixed with at least one lubricant and/or with at least one disintegrant, is filled into capsules or sachets or is pressed into tablets.

SUBSTITUTE SHEET